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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/509,994	05/08/2000	MASAKI YUI	KP-8753	9126

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EXAMINER	
SCHNIZER, HOLLY G	
ART UNIT	**PAPER NUMBER**
1653	15

DATE MAILED: 02/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

FILE COPY

Office Action Summary	Application No.	Applicant(s)	
	09/509,994	YUI ET AL.	
	Examiner	Art Unit	
	Holly Schnizer	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 November 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 May 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of the Claims

The Amendment and Response filed November 27, 2002 has been entered and considered. Claims 1-21 have been cancelled and Claims 22-46 have been added. Claims 22-46 are currently pending and have been considered on the merits in this Office Action.

Claim Objections and Rejections Withdrawn

The Objection/rejections of claims 1-21 is moot in view of the cancellation of the claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 22-35 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 22-35 are indefinite as to what is being claimed. Is it a method of maintaining a thrombomodulin solution or a method of preparing a thrombomodulin solution. The claims are drawn to "a method for maintaining an aqueous injection preparation of thrombomodulin" yet there is only one step involving preparation of an

aqueous solution of thrombomodulin and there is no endpoint to determine whether the method has achieved its goal. What actual steps, besides preparing the thrombomodulin solution, are necessary to "maintain" a solution, and what measurable value indicates that the thrombomodulin solution has been maintained? To maintain a preparation implies that the preparation is stored in a certain condition for a given length of time yet the claims do not recite any steps of storing the preparation prepared in step 1 and the claims do not indicate what condition is maintained. Clarification is required.

Applicants contend that the rejection has been overcome because the term "quality" has been omitted by the newly added claims. However, this omission does not clarify whether the claim is drawn to a method of maintaining (i.e. storing) a preparation (and if so, the condition (i.e. properties) of the preparation that is to be "maintained" by the claimed method) or a method of preparing a thrombomodulin preparation. Thus, clarification is still required and the rejection is maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 22-29 and 35-46 are rejected under 35 U.S.C. 102(b) as being anticipated by Kunihiro et al. (U.S. Patent No. 5,202,421, Apr. 1993).

The rejection will be repeated below as it applies to the new claims followed by a response to Applicants arguments.

Rejection:

Kunihiro et al. a thrombomodulin solution and method of its preparation having identical steps to that of the present claims. Since the Kunihiro et al. reference discloses methods with identical steps, it would be inherent that the method would produce identical results as the present invention. Kunihiro et al. describe preparing the thrombomodulin as an aqueous solution having a pH of 7.0 (in the range of 5-7.0) and a phosphate buffer (buffer component)(clm 29) that has buffering action in the pH range of 5 and 7.0. The aqueous solution of thrombomodulin also has a surfactant (LUBROL TM) and is contained in a container (see Col. 9, lines 43-48). The thrombomodulin peptides used in the experiments disclosed by Kunihiro et al. had molecular weights of 72,000, 79,000, 94,000, and 114,000 as determined by SDS-PAGE gel electrophoresis in non-reduced state (Col. 4, lines 54-65)(clm 26). The soluble thrombomodulin of Kunihiro et al. exhibits the function for accelerating the activation of protein C by thrombin and consists of a thrombomodulin which is constituted of an amino acid sequence composed of those amino acid residues in which one or more amino acid residues in the amino acid sequence of SEQ ID NO:1 are replaced or removed or one or more amino acid residues are added thereto (see present clm. 27, part ii). The thrombomodulin solutions of Kunihiro et al. are preferably administered by injection (Col. 10, line 57). The thrombomodulin solutions of Kunihiro et al. would meet the limitations of Claims 36-39 and 41-45 because they contain all of the components of the

compositions of the claims as explained above (thrombomodulin, buffer component at pH 5-7, surfactant and aseptic. It is noted that Claims 36-39 and 41-45 are drawn to compositions and not an apparatus (a syringe, container, etc.). Thus, absent evidence that the components of a composition change with the container they are placed in, the claims drawn to compositions contained in syringes would not be patentably distinguishable from those of Kunihiro et al.

Kunihiro et al. also provide an example of an injection preparation containing 2 mg/ml and 4 mg/ml of thrombomodulin (Col. 12, Example 2 and 3) therefore Kunihiro et al. meets the limitations of claim 46. Kunihiro et al. state that "[t]he above components were dissolved in 10 mL of distilled water for injection. The obtained solution was sterilized by filtration, and 1.0 mL each of this solution was put into sterilized vials" (Col. 12, lines 20-23). While Kunihiro et al. teaches that the solutions were later freeze-dried, the aqueous solutions made prior to freeze-drying are patentably indistinguishable from the compositions of claims 36-39 and 41-46.

Response to Applicants arguments:

Applicants argue that Kunihiro et al. fail to disclose or suggest an aqueous soluble thrombomodulin can be stored or transported without losing its activity or without change of appearance or turbidity when stored for a long time or when shaken.

This argument has been considered but is not deemed persuasive because as explained above and in the previous Office Action, Kunihiro et al. teach all of the steps of the claimed methods and all of the components of the claimed compositions. Therefore, it would be inherent that a method such as Kunihiro et al. having identical

steps to the claimed invention would have identical endoint/result (same properties after storage or shaking) and it would be inherent that a composition having identical components would have identical properties. Therefore, absent a step that is unique to the claimed invention or a component unique to the composition of the claimed invention, the claims are unpatentable over Kunihiro et al. (The examiner also notes that the claimed methods do not require that the thrombomodulin solution maintains activity, appearance, or turbidity upon storage or shaking and in fact does not require that the thrombomodulin solution be stored or transported (shaken).

Applicants argue that Kunihiro et al. do not teach that surfactant is added to soluble thrombomodulin (TM1) but only to insoluble human placental thrombomodulin.

This argument has been considered but is not deemed persuasive for the following reasons. The claimed methods do not require that the surfactant be added to a soluble thrombomodulin. In fact, the only step in the method is preparing an aqueous solution (the claims do not include a step of adding a surfactant). The claims only indicate that the solution that is prepared comprises soluble thrombomodulin and may also comprise a surfactant (see part (a) of Claim 22 for example). In addition, Claims 22, 24, 26-27, 29-30 do not require surfactant but only that the aqueous solution is in the form of a prefilled syringe preparation and said prefilled syringe preparation is packed aseptically in a syringe so as to exclude any substantial gas space therein. Since Kunihiro et al. teach that TM1 was injected (Col. 9, lines 60-64), it is inherent that the TM1 solution injected was packed aseptically in a syringe so as to exclude any

substantial gas space therein, and routine practice in the art to ensure that syringes (when filled with material for injection) contain a minimal amount of air space.

Therefore, for the reasons provided above and in the previous Office Action, the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 22-29, 31-33, and 35-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kunihiro et al. (U.S. Patent No. 5,202,421, Apr. 1993 in view of Nursing Procedures (Charnow et al. eds., Springhouse Corp. Springhouse, PA, 1993, pp. 286-287).

The teachings of Kunihiro have been discussed above and teach the claimed thrombomodulin preparations and the methods of making them.

Kunihiro et al. do not specifically teach that the syringe containing the disclosed thrombomodulin preparation was packed so as to exclude any substantial gas space therein.

Nursing Procedures teaches the risks and deleterious effects of injecting air into the body. Air embolisms (caused by injecting air into the veins) result in respiratory distress, weak pulse, decreased blood pressure, and loss of consciousness and Nursing Procedures implies that care should be taken to completely remove air from the injection device (see Risks of I.V. Therapy, Air embolism, p. 286 and Col. 2, p. 287).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to practice the method of making the thrombomodulin preparation as taught in Kunihiro et al. wherein the preparation was packed into syringes so as to minimize the amount of gas space in the syringe). The thrombomodulin solutions of Kunihiro et al. are administered by injection (Col. 10, line 57) and Nursing Procedures emphasizes the importance of removing air from syringes when preparing for injections. Therefore, one of ordinary skill at the time of the invention would have been motivated to "exclude any substantial gas space" from the syringe to minimize the occurance of any air embolisms upon injection of the preparation into the patient. Thus, the claims are unpatentable over the prior art.

Objections

Claim 28 is objected to for the recitation of "a DNA segment decoding an amino acid sequence" in line 8 of the claim. DNA does not "decode" an amino acid sequence. The examiner suggests deleting "decoding" and replacing it with "encoding".

Conclusions

No Claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Holly Schnizer whose telephone number is (703) 305-3722. The examiner can normally be reached on Monday through Wednesday from 8 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (703) 308-2923. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703 308-0196.

Holly Schnizer
February 19, 2003

KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER